

# BMJ Open Multiarm, non-randomised, single-centre feasibility study – investigation of the differential biology between benign and malignant renal masses using advanced magnetic resonance imaging techniques (IBM-Renal): protocol

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## ABSTRACT

**Introduction** Localised renal masses are an increasing burden on healthcare due to the rising number of cases. However, conventional imaging cannot reliably distinguish between benign and malignant renal masses, and renal mass biopsies are unable to characterise the entirety of the tumour due to sampling error, which may lead to delayed treatment or overtreatment. There is an unmet clinical need to develop novel imaging techniques to characterise renal masses more accurately. Renal tumours demonstrate characteristic metabolic reprogramming, and novel MRI methods have the potential to detect these metabolic perturbations, which may therefore aid accurate characterisation. Here, we present our study protocol for the investigation of the differential biology of benign and malignant renal masses using advanced MRI techniques (IBM-Renal).

**Methods and analysis** IBM-Renal is a multiarm, single-centre, non-randomised, feasibility study with the aim to provide preliminary evidence for the potential role of the novel MRI techniques to phenotype localised renal lesions. 30 patients with localised renal masses will be recruited to three imaging arms, with 10 patients in each: (1) hyperpolarised [ $^{13}\text{C}$ ]-pyruvate MRI, (2) deuterium metabolic imaging (DMI) and (3) sodium MRI. The diagnosis will be made on samples acquired at biopsy or at surgery. The primary objective is the technical development of the novel MRI techniques, with the ultimate aim to understand whether these can identify differences between benign and malignant tumours, while the secondary objectives aim to assess how complementary the techniques are, and if they provide additional information. The exploratory objective is to link imaging findings with clinical data and molecular analyses for the biological validation of the novel MRI techniques.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first prospective study to investigate the role of deuterium metabolic imaging and sodium MRI for the characterisation of indeterminate renal masses.
- ⇒ A patient can be recruited into different imaging arms of the study, thus allowing for direct comparison of novel MRI techniques for informing about the nature of the renal masses.
- ⇒ Multimodal assessment of these renal masses, including clinical, imaging and pathology data, will be conducted.
- ⇒ Limitations of the study include potential pathological undergrading of benign renal masses, as some of these diagnoses are based on a single biopsy.
- ⇒ If the primary outcomes are met, this will be used to inform a large-scale study.

**Ethics and dissemination** This study was ethically approved (UK REC HRA: 22/EE/0136; current protocol version 2.1 dated 11 August 2022). The plans for dissemination include presentations at conferences, publications in scientific journals, a doctoral thesis and patient and public involvement.

**Trial registration number** NCT06016075.

## INTRODUCTION

### Clinical need in management of localised renal masses

The incidence of renal cancer has increased significantly during the last two decades, with 13 322 new cases diagnosed annually in the

UK, corresponding to an age-standardised incidence of 8.2 per 100 000.<sup>1</sup> Depending on histological subtype and other tumour-related and patient-related factors (such as tumour location, complexity, patient comorbidities, surgical history, renal function), the management options range from active surveillance to radical surgical resection.<sup>2</sup> An important unmet clinical need is that conventional imaging methods cannot reliably distinguish aggressive renal cell carcinoma (RCC) subtypes from indolent renal masses.<sup>3</sup> Although an invasive renal mass biopsy is a key tool for distinguishing radiologically indeterminate renal lesions, it is subject to sampling error, which is particularly problematic in heterogeneous lesions. Biopsies may also be clinically challenging to perform and are non-diagnostic in up to 20% of cases, which can result in either unnecessary or delayed surgery.<sup>4–7</sup> Importantly, earlier detection and treatment have not resulted in decreased mortality, suggesting that there is an overdiagnosis and potentially overtreatment of benign renal tumours.<sup>1 8</sup> As RCC remains one of the most lethal urological malignancies,<sup>9</sup> there is a pressing need for novel methods to identify and characterise renal masses more accurately.<sup>10</sup>

### Metabolic changes in RCC

Renal cell tumours harbour significant metabolic perturbations and different histologic subtypes have distinct metabolic phenotypes. In clear cell RCC (ccRCC), the major genetic driver is the loss of the von Hippel-Lindau tumour suppressor gene, which leads to accumulation of hypoxia-inducible factor 1 $\alpha$  with downstream transcriptional activation of pathways involved in glycolysis.<sup>11 12</sup> Metabolomic analyses have confirmed increased lactate labelling after [U-<sup>13</sup>C]glucose infusion in ccRCC tumours compared with adjacent normal kidney with glycolysis increasing in a grade-dependent manner.<sup>13–15</sup> On the other hand, renal oncocytomas, which are classified as benign renal masses, suppress oxidative metabolism due to defective complex I within the mitochondrial electron transport chain.<sup>11 16–18</sup> Therefore, it is not clear to what extent the ratio between glycolytic and oxidative metabolism varies across aggressiveness of renal neoplasms.<sup>17 19</sup> Recently, studies have also reported mitochondrial respiration defects in both renal oncocytoma and its malignant counterpart, chromophobe RCC (chRCC), with the potential for differentiation based on genomic, transcriptomic and metabolic levels.<sup>16 17 20</sup> The question to be addressed in this study is whether MRI can be used to phenotype the aggressiveness of renal masses, and can therefore implement to help risk-stratify tumours to inform management decisions.

### Imaging metabolism

Building on the evidence described above, we hypothesise that novel MRI techniques can non-invasively characterise whole-tumour metabolism and its heterogeneity across renal tumours. The most common clinical tool for assessment of tumour metabolism uses a radiolabelled glucose

analogue, in conjunction with positron emission tomography, but its effectiveness is limited by renal excretion of the tracer, and it has failed to show success in characterising renal tumours.<sup>21 22 99mTc-sestamibi</sup> in conjunction with single-photon emission CT has been used to detect a variable degree of tracer uptake in renal oncocytoma compared with chRCC in a small number of patients, which has been attributed to the tracer accumulation in cells with high levels of mitochondria.<sup>23 24</sup> However, both techniques expose patients to ionising radiation, offer poor soft tissue contrast and the inability to detect specific downstream metabolites or their metabolic compartmentalisation.<sup>25 26</sup>

Our multidisciplinary group are developing novel non-radioactive and non-invasive clinical tools for imaging tumour metabolism. For example, hyperpolarised [<sup>1-13</sup>C]-pyruvate MRI (HP <sup>13</sup>C-MRI), following injection of intravenous hyperpolarised <sup>13</sup>C-pyruvate, can be used to simultaneously detect glycolytic metabolism in the cytosol and oxidative metabolism in the mitochondria in tissue where there is sufficient metabolism.<sup>27</sup> Two recent papers have shown that <sup>13</sup>C-lactate labelling can be used to distinguish high-grade ccRCC from lower-grade tumours, driven by the pyruvate transporter (monocarboxylate transporter 1; MCT1).<sup>28</sup> Furthermore, a case of a renal oncocytoma displayed the lowest pyruvate-to-lactate conversion compared with a range of malignant masses, including ccRCCs, suggesting that this may be a tool for discriminating these lesions.<sup>28</sup>

More recently, we have implemented deuterium (<sup>2</sup>H) metabolic imaging (DMI) at clinical field strength as an alternative method for non-invasive detection of metabolism using orally administered deuterated glucose.<sup>29</sup> This method can also be used to detect cytosolic lactate formation and mitochondrial oxidative metabolism, and is complementary to the information provided by HP <sup>13</sup>C-MRI.<sup>30 31</sup> We have undertaken this in the brain at clinical field strength (3T) and will apply it to the kidney in this study using dedicated hardware to assess whether differential glucose metabolism can be used to differentiate benign from malignant lesions.

### Imaging cellularity and structure

To complement the metabolic measurements, we will evaluate non-invasive methods to distinguish benign from malignant lesions based on differences in cellularity on histology. Sodium MRI (<sup>23</sup>Na-MRI) is a complementary tool to probe tissue structure as a measure of the tissue sodium concentration, which is a function of cellularity due to the concentration gradient across the cell membrane. The method can also be used to extract an intracellular-weighted component of the sodium pool as a measure of the transmembrane sodium gradient.<sup>32</sup> In the presence of hypoxia, the sodium/potassium ATP pump may be inhibited, leading to alterations in the sodium concentration.<sup>32 33</sup> We have previously shown how <sup>23</sup>Na-MRI can be used to demonstrate the Na<sup>+</sup> gradient across the corticomedullary axis in the normal kidney

and how this can be used to assess dynamic changes in renal sodium.<sup>33</sup> We have also recently developed a novel birdcage MRI coil system for high resolution <sup>23</sup>Na-MRI of the normal kidneys,<sup>34</sup> which we will apply to imaging focal renal pathology as part of this study. We have shown the potential of <sup>23</sup>Na-MRI in several cancer types, correlating with cellularity on histology, and will apply this to small renal masses for the first time here.<sup>35 36</sup>

In addition, we have developed complementary <sup>1</sup>H-MRI methods to quantitatively map T2 relaxation properties within tissue for assessment of diffuse renal disease.<sup>37</sup> Here, we will assess whether these can distinguish benign from malignant lesions. These parameters are dependent on the local tissue chemical properties and reflect the microenvironmental differences between benign and malignant disease.

### Rationale for the study

This feasibility study will explore the role of multimodal MRI in characterising localised renal masses and how it can exploit the known biological differences between benign and malignant lesions. The project will assess if MRI can probe structure, function and metabolism within the tumour and its microenvironment using three techniques:

1. HP <sup>13</sup>C-MRI as a non-invasive measure of tissue metabolism following injection of hyperpolarised <sup>13</sup>C-pyruvate to probe tumour lactate labelling.
2. DMI as an alternative method to probe both glycolytic and oxidative metabolism following oral <sup>2</sup>H-labelled glucose to detect both lactate and the combined signal from glutamine+glutamate.
3. Measures of the tumour cellularity, heterogeneity and membrane ion gradients using <sup>23</sup>Na-MRI and fast, high-resolution measures of T2 relaxation.

The aim is to provide preliminary evidence for the potential role of these techniques to phenotype localised renal lesions and how they can be used as part of a larger multicentre study. The ultimate goal is to provide non-invasive tools for early detection of small, aggressive renal tumours to enable timely surgical intervention.

### METHODS AND ANALYSIS

The study is reported in accordance to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist,<sup>38</sup> with SPIRIT-Path extension.<sup>39</sup>

### Study design and objectives

The investigation of differential biology of benign and malignant renal masses using advanced MRI techniques study is designed as a feasibility study to acquire preliminary data with set imaging protocols as defined based on our previous work, and these results will be used to optimise future imaging protocols and to inform large-scale studies. The study will be conducted as a non-randomised, physiological imaging study in patients with localised renal masses, at a single site: Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust. For all imaging studies, the primary objective will be the technical development of each imaging technique with ultimate aim to understand whether the methods can identify any differences between benign and malignant tumours, including measuring the <sup>13</sup>C-pyruvate-to-lactate conversion with HP <sup>13</sup>C-MRI, quantifying sodium concentration using <sup>23</sup>Na-MRI, detecting <sup>2</sup>H-glucose and its metabolites using DMI. Secondary objectives will aim to compare the imaging techniques to understand if they can produce complementary information. As an exploratory part of the study, the objective will be to link the imaging data with clinical data and tissue molecular analyses for biological validation of the novel MRI techniques. Diagnostic accuracy analysis is not foreseen at this stage.

### Participant selection

Participants will be identified through multidisciplinary team meetings or by clinical teams involved in their routine care at Addenbrooke's Hospital, and recruited if they meet all the inclusion and none of the exclusion criteria as detailed in table 1. The participants will be allocated into three imaging arms with 10 patients in each: (1) HP <sup>13</sup>C-MRI; (2) DMI; and (3) <sup>23</sup>Na-MRI. <sup>1</sup>H-MRI with T2-mapping will be performed in all patients. The recruited participant will be allocated to one of these

**Table 1** Inclusion and exclusion criteria for selection of study participants

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>▶ Over 18 years old.</li> <li>▶ Able to and provide written informed consent to participate.</li> <li>▶ If female: postmenopausal or if a woman of childbearing potential using a suitable contraception.</li> <li>▶ If male, using a suitable contraceptive method for the duration of the study.</li> <li>▶ Radiologically suspected or pathologically confirmed benign or malignant renal masses, as determined by standard clinical practice.</li> <li>▶ Capable of undergoing a minimum of one study visit.</li> </ul>	<p>The presence of any of the following will preclude participation, as determined by the delegated investigator:</p> <ul style="list-style-type: none"> <li>▶ Contraindication or inability to tolerate MRI.</li> <li>▶ Pregnant or actively breastfeeding woman.</li> <li>▶ If using an intrauterine contraceptive device as a method of contraception, the device should be MRI safe at 3 T (researcher to confirm).</li> <li>▶ Clinically significant cardiac, pulmonary or neurological diseases as determined by the investigators.</li> <li>▶ Laboratory abnormalities that may impact on the study results.</li> <li>▶ Any other significant medical or psychiatric history rendering the subject ineligible as deemed by the investigators.</li> </ul>

imaging techniques by the chief investigator. This will be based on the availability of kits for HP  $^{13}\text{C}$ -MRI, availability of the deuterated glucose drink for the DMI study and/or availability of the research MRI scanner. The aim is to recruit at least four patients in each arm with an oncocyctic renal neoplasm (mostly oncocytomas) and at least four patients with RCCs as determined by clinical pathology assessment to enable direct comparison. Half of the patients in each arm will be selected from a cohort of newly diagnosed renal masses and imaged prior to biopsy, with 75%–80% of these expected to have RCCs, and most of the remainder having oncocyctic neoplasms. The other half will be acquired from retrospective cohorts of patients with previously diagnosed oncocyctic neoplasms on active surveillance at least 6 weeks post biopsy. Diagnosis will be made on tissue samples acquired at biopsy or at surgery if applicable, using molecular markers where possible. This approach will ensure an appropriate balance between benign and malignant lesions in each cohort.

Participants may be removed from the study at their choice or at the investigator's discretion if it is felt to be clinically appropriate. Reasons for participant withdrawal will be recorded. Primary reasons for withdrawal may include serious adverse event (SAE), withdrawal of consent, lost to follow-up, participant non-compliance, or study closed or terminated. Participants who are withdrawn from the study or do not complete at least one scan will be replaced.

### Interventions

Study participants will be deemed evaluable if they receive at least one scan on any of the three imaging techniques. Each study participant will be allocated a unique study number following study enrolment and will be identified by this number throughout the data collection and analysis process.

The participants will be asked to attend all or some of these timepoints:

1. Baseline imaging visit.
2. An optional repeat scan within 7 days of the first scan using the same imaging technique.
3. For those not taking part in part 2 above, an optional scan with another imaging technique within 14 days of the first scan. The second imaging arm will be determined as detailed above; that is, by the chief investigator based on the availability of the imaging kits and the research MRI scanner.
4. An optional research biopsy will be undertaken at standard of care surgery or at biopsy, whichever will be clinically indicated and performed.

The study flow chart is presented in [figure 1](#).

[Table 2](#) provides an overview of assessments to be performed at each study visit.

For participants with benign renal masses that subsequently undergo active surveillance and have repeated MRI scans, we will seek the permission from the participants to review the clinically required MRI scan and compare to what was collected at the research scan. If the

participant is not due to have a clinically required MRI scan, the research team will not affect this decision.

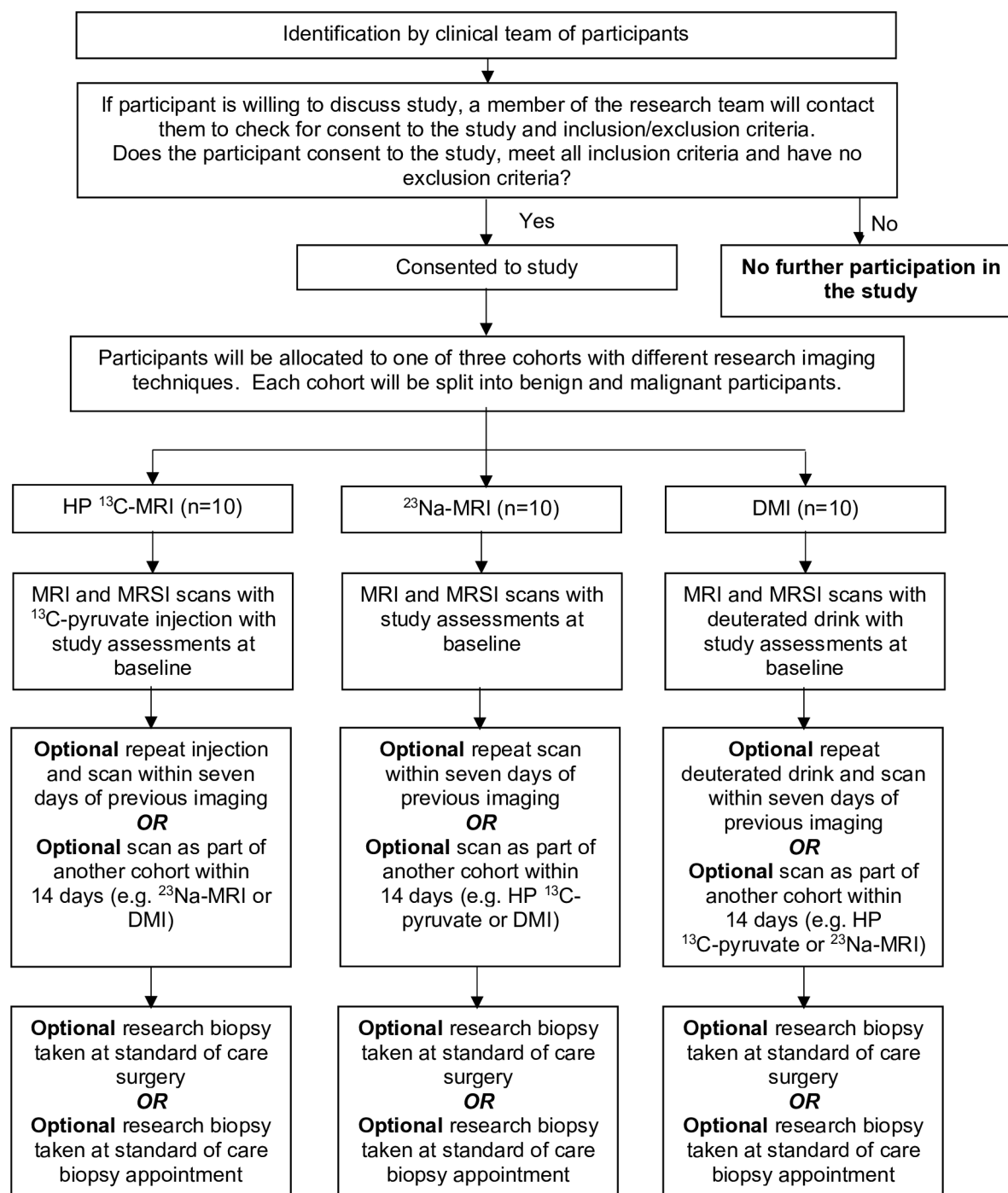
We will endeavour to minimise the number of injections and/or deuterated drinks for each participant, in as, the maximum number of injections/drinks will be limited to two each. Routes of administration for each of the imaging agents are as following:

1. HP  $^{13}\text{C}$ -MRI: single intravenous injection of up to 40 mL at 0.4 mL/kg of  $^{13}\text{C}$ -pyruvate through an intravenous cannula while the study participant is in position on the scanner bed. Scanning will begin 12s after the injection. There will be an optional repeat injection of  $^{13}\text{C}$ -pyruvate at all imaging visits to test for repeatability of the  $^{13}\text{C}$ -MRI technique. These will take place within 7 days of the first scan.
2.  $^{23}\text{Na}$ -MRI: not applicable. No additional research probe will be given to the participant as part of this imaging technique.
3. DMI: at each imaging visit, the participant will receive a deuterated glucose solution where 60 g of glucose is dissolved in 200 mL of water for injection and the dose solution will be adjusted to their body weight at 0.75 g/kg body weight. Scanning will begin 60 min after the drink ingestion. There will be an optional repeat deuterated drink at all imaging visits to test for repeatability of the DMI technique. These will take place within 7 days of the first scan.

### The sample size calculation and outcomes

The study has been powered to assess changes in the  $^{13}\text{C}$ -pyruvate metabolism from the data we collected from nine treatment-naïve renal tumour patients.<sup>28</sup> This work showed that the median pyruvate-to-lactate conversion constant ( $k_{\text{PL}}$ ) in ccRCCs was 0.0065 (range 0.0024–0.0151), while it was 0.0043 (range 0.0028–0.0076) in the normal kidney. This study also reported metabolism in a single case of renal oncocytoma, which showed both the lowest conversion constant and lactate-to-pyruvate ratio (LAC/PYR). There are currently no published studies assessing DMI and  $^{23}\text{Na}$ -MRI quantitative parameters in human kidney tumours.

Based on the parameters obtained from the HP- $^{13}\text{C}$ -MRI, pragmatic sample sizes have been determined for priming of the study: we plan to include up to 30 participants in total: 15 with benign renal masses and 15 with malignant renal masses. These participants will be divided equally into three imaging arms (HP  $^{13}\text{C}$ -MRI,  $^{23}\text{Na}$ -MRI and DMI); therefore five benign and five malignant participants will be recruited to each imaging arm. If participants are willing to take part in the optional additional scan using a different imaging technique, these participants will be counted towards both arms of the study and therefore the total number recruited to the study will be less than 30 participants. The planned timeline for the study is as follows: start date on 1 January 2023, primary completion date on 31 August 2025, with study completion by 1 January 2026.



**Figure 1** Study flow chart. DMI, deuterium metabolic imaging; HP <sup>13</sup>C-MRI, hyperpolarised [1-<sup>13</sup>C]-pyruvate MRI; MRSI, magnetic resonance spectroscopy imaging; <sup>23</sup>Na-MRI, sodium MRI.

Descriptive statistics will be used. The primary covariates to be studied are as follows:

1. HP-<sup>13</sup>C-MRI: ratio of the summed hyperpolarised <sup>13</sup>C-lactate to the summed <sup>13</sup>C-pyruvate over the timecourse of the experiment as a quantitative metric of pyruvate-to-lactate exchange catalysed by the enzyme lactate dehydrogenase. This metric is termed the LAC/PYR. We have significant experience in developing quantitative methodology to analyse this data.<sup>40</sup>
2. <sup>23</sup>Na-MRI: total sodium concentration, as a metric to quantify accumulation of Na<sup>+</sup> in the tissue of interest.

This metric was used in comparison between prostate cancer and normal prostate tissue.<sup>35</sup>

3. DMI: primary goal is the technical development of the abdominal DMI, which has not been extensively developed yet due to limitations in detection of metabolites within the DMI spectrum in abdomen attributed to lipid peaks and variability of tissues. However, we aim to evaluate the ratio of the summed <sup>2</sup>H-lactate over the summed combined signal from <sup>2</sup>H-glutamine+<sup>2</sup>H-glutamate as a measure of the ratio of glycolysis to oxidative metabolism, as previously shown in healthy human brain.<sup>41</sup>

**Table 2** Schedule of assessments

Assessment	Visit/days			
	Screening†	Baseline MRI visit	Optional repeat MRI visit within 7 days of baseline (if applicable)	Optional MRI visit with different imaging technique within 14 days of baseline (if applicable)
Attend unit	*	*	*	*
Consent‡	*	*	*	*
Medical history	*			
Demography (weight, height, sex, date of birth)	*			
Clinical examination	*			
ECOG performance score	*	* if clinically indicated	* if clinically indicated	* if clinically indicated
Venous blood sample§¶	*	*	*	*
Pregnancy test in WOCBP	*	*	*	*
MRI scan		*	*	*
General/additional assessments		* if clinically indicated	* if clinically indicated	* if clinically indicated
Vital signs				
Pre imaging		*	*	*
Post imaging		*	*	*
Injection of <sup>13</sup> C-pyruvate and/or deuterated glucose drink (for <sup>13</sup> C-pyruvate and DMI techniques only)		*	*	*

\*Applicable assessment.  
†We will attempt to screen for participants during their standard of care visits and use of medical records.  
‡Ongoing consent will be confirmed at each visit.  
§Venous blood samples will include, but may not be limited to; biochemical series and liver function test.  
¶Full blood count samples will only be required at injection timepoints if they have not been taken recently, that is, within 14 days. These results will be copied in the study data.  
DMI, deuterium metabolic imaging; ECOG, Eastern Cooperative Oncology Group; WOCBP, woman of childbearing potential.

## Data management and confidentiality

### Case report form (CRF)

All data collected during the study will be collected or transferred into the CRF, which will be anonymised. All study data in the CRF must be extracted from, and be consistent with, the relevant source documents. The CRFs must be completed, dated and signed by the investigator or designee in a timely manner. The CRF will be accessible to relevant study team members, study monitors, auditors or inspectors as required.

### Data protection and participant confidentiality

All investigators and study site staff involved in this study must comply with the requirements of the General Data Protection Regulation 2018 and Trust Policy with regard to the collection, storage, processing and disclosure of personal information and will uphold core principles. The personal data recorded on all documents will be regarded as strictly confidential.

### Study documentation and archiving

All essential source and study documentation including the study master file, source data and pro forma will be securely

archived after the last analysis of the study data has been completed, and the final study report has been submitted to the relevant authorities. Archiving must be provided as per local policy or the length of time specified by current applicable legislation, whichever is the longer. The investigator must not destroy any documents or records associated with the study without written approval from the sponsor.

## Ethics and dissemination

### Ethical and regulatory considerations

Following the application through the Integrated Research Application System (IRAS, number: 314155), this study with related documentation has been approved by the East of England—Cambridge East Research Ethics Committee (REC), Health Research Authority (HRA), receiving the REC reference: 22/EE/0136. The Research & Development Department of Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge act as sponsors for this research project with respect to the UK Policy Framework for Health and Social Care Research. Further ethical and regulatory considerations are detailed below.

## Informed consent form

The informed consent form was approved by the REC and is in compliance with good clinical practice (GCP), local regulatory requirements and legal requirements. The investigator must ensure that each study participant, or their legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with their participation. The suitably trained investigator will obtain written informed consent from each participant before any study-specific activity is performed. The investigator will retain the original of each signed informed consent form.

## REC review

Before the start of the study or implementation of any amendment, we will obtain approval of the study protocol, protocol amendments, informed consent forms and other relevant documents, for example, advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the study master file.

## Regulatory issues

This study is not a Clinical Trial of an Investigational Medicinal Product, as defined by the European Union Directive 2001/20/EC, and no submission to the Clinical Trials Unit at the Medicines and Healthcare products Regulatory Agency is required.

## Protocol amendments

Protocol amendments must be reviewed and agreed by the sponsor prior to submission to the REC/HRA. The only circumstance in which an amendment may be initiated prior to REC/HRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (urgent safety measures). In this case, accrual of new participants will be halted until the REC/HRA approval has been obtained.

## Declaration of Helsinki and GCP

The study will be performed in accordance with the spirit and the letter of the Declaration of Helsinki, the conditions and principles of GCP, the protocol and applicable local regulatory requirements and laws.

## GCP training

All study staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this study. This training should be updated every 2 years or in accordance with Cambridge University Hospitals NHS Foundation Trust policy.

## Safety considerations

### Adverse reactions (ARs)/expected adverse events (AEs)

There are no expected ARs associated with  $^{13}\text{C}$ -pyruvate and deuterated glucose MRI. If any ARs are observed during this study, they will be recorded on the pro forma and reviewed by the research team.

The following AEs are known side effects of the assessment procedures:

1. Bruising at the sites of venepuncture.
2. For those participants having the  $^{13}\text{C}$ -pyruvate injection, a transient local reaction at site of injection, a transient change in taste and mild flushing.

They are generally not serious in nature and will not be recorded in the AE/AR log as part of this study.

Participants with solid malignancies are expected to have cancer and treatment related AEs and some of them may be SAEs. However, as these are related to cancer rather than the study procedures, they will not be recorded or collected as study data during this study. Only study procedure related SAE will be recorded.

## Recording, evaluation and reporting of AEs

The sponsor expects that all AEs are recorded from the point of informed consent.

All AR/AEs will be assessed by the investigator and recorded in medical notes as well as on the pro forma (except for expected AEs and SAEs related to cancer).

Individual AEs should be evaluated by the investigators. This includes the evaluation of its seriousness, causality, severity and any relationship between the medicinal product(s) and/or concomitant therapy and the AE.

The chief investigator is responsible for the prompt notification to the sponsor and the REC that gave a favourable opinion of the study where in the opinion of the chief investigator the event was:

1. 'Related': that is, it resulted from administration of any of the research procedures.
2. 'Unexpected': that is, the nature and severity of the event is not listed in the protocol or the investigator's brochure as an expected occurrence.

Reports of related and unexpected SAEs should be submitted to the sponsor and the REC within 15 days of the chief investigator becoming aware of the event.

## Toxicity—emergency procedures

No toxicity is expected as both pyruvate and glucose are endogenous products. However, in the event of an acute hypersensitivity reaction, supportive care will be given to the participant according to local clinical procedures.

## Patient and public involvement (PPI)

Patient representative groups were closely involved in preparation of the study protocol. We have sought help from the Cambridge University Hospitals PPI Panel, who kindly reviewed the study documentation we were intending to submit with the IRAS for the REC review. With their valuable feedback, we have adapted documentation to make it easier to follow, such as developing graphic representations of the study procedures and preparing separate documents for each of the imaging arms.

## Dissemination plans

The clinical and feasibility data are expected to be of great interest to the uro-oncological community, including

radiologists, pathologists, surgeons and oncologists. Results will be reported internally, presented at conferences, published in peer-reviewed scientific journals and will constitute a part of a PhD thesis. Further, we will engage patients and the public by organising workshops reporting the findings of the study and presenting at the public engagement festivals.

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**Contributors** FAG is the chief investigator and initiated the collaborative project. IH-M and MJL conceptualised the study, developed the study design, drafted and revised the study protocol and documentation. IH-M and MJL-M monitored data collection and drafted the paper. MW is the study coordinator, provided management oversight and monitored data collection. JK, ASK, JD, ABG, ANP, HL and MAM contributed to the study design and statistical analysis plan. IM, AYW, SJW, JOJ, JNA, TJM and GDS provided clinical expertise for the study design. All authors revised the paper. FAG is the guarantor.

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**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods and analysis section for further details.

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